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Aspirin Impairs Reverse Myocardial Remodeling in Patients With Heart Failure Treated With Beta-Blockers

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OBJECTIVES We hypothesized that aspirin (ASA) might alter the beneficial effect of beta-blockers on left ventricular ejection fraction (LVEF) in patients with chronic heart failure.

BACKGROUND Aspirin blunts the vasodilation caused by both angiotensin-converting enzyme (ACE) inhibitors and beta-blockers in hypertensive patients and in patients with heart failure. Several studies suggest that ASA also blunts some of beneficial effects of ACE inhibitors on mortality in patients with heart failure. To our knowledge, there have been no data evaluating the possible interaction of ASA and beta-blockers on left ventricular remodeling in patients with heart failure.

METHODS We retrospectively evaluated patients entered into the Multicenter Oral Carvedilol Heart failure Assessment (MOCHA) trial, a 6-month, double-blind, randomized, placebo-controlled, multicenter, dose-response evaluation of carvedilol in patients with chronic stable symptomatic heart failure. Multivariate analysis was performed to determine if aspirin independently influenced the improvement in LVEF.

RESULTS Over all randomized patients (n = 293), LVEF improved 8.2 ± 0.8 ejection fraction (EF) units in ASA nonusers and 4.5 ± 0.7 EF units in ASA users (p = 0.005). In subjects randomized to treatment with carvedilol (n = 231), LVEF improved 9.5 ± 0.9 EF units in ASA nonusers and 5.8 ± 0.8 EF units in ASA users (p = 0.02). In subjects randomized to treatment with placebo (n = 62), LVEF improved 2.8 ± 1.2 EF units in ASA nonusers and 0.5 ± 1.4 EF units in ASA users (p = 0.20). Aspirin did not significantly affect the heart rate or systolic blood pressure response in either the placebo or carvedilol groups. The effect of ASA became more significant on multivariate analysis. The change in LVEF was also influenced by carvedilol dose, etiology of heart failure, baseline heart rate, EF and coumadin use. The detrimental effect of ASA on the improvement in LVEF was dose-related and was present in both placebo and carvedilol groups, although the effect was statistically significant only in the much larger carvedilol group.

CONCLUSIONS Aspirin significantly affects the changes in LVEF over time in patients with heart failure and systolic dysfunction treated with carvedilol. The specific mechanism(s) underlying this interaction are unknown and further studies are needed to provide additional understanding of the molecular basis of factors influencing reverse remodeling in patients with heart failure.
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Considerable controversy exists as to whether aspirin (ASA) blocks some of the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors in patients with chronic heart failure (1). Several studies demonstrate that ASA attenuates the acute hypotensive effects of ACE inhibitors in patients with hypertension as well as the acute vasodilator effect of ACE inhibitors in patients with heart failure (2–6). Retrospective analyses of both the Studies Of Left Ventricular Dysfunction (SOLVD) study and Cooperative New Scandinavian Enalapril Survival Study II suggested either absent or reduced beneficial effects, respectively, of enalapril in patients taking ASA (7,8). However, other studies have not demonstrated an interaction between ACE inhibitors and ASA (9–12). To our knowledge, no other studies have evaluated whether there is an interaction between ASA and beta-blockers in patients with heart failure. It is known that ASA attenuates the hypotensive but not the negative inotropic or chronotropic effects of beta-blockers and it has been suggested that this effect may be prostaglandin (PG)-mediated (13). We postulated that ASA might interact with beta-adrenergic blockers in patients with chronic heart failure. As an improvement in left ventricular ejection fraction (LVEF) is a consistent therapeutic benefit in patients with heart failure treated with beta-blockers, we evaluated the effect of ASA on the improvement in LVEF in patients who had participated in the Multicenter Oral Carvedilol Heart failure Assessment (MOCHA) trial, a study that compared multiple doses of carvedilol to placebo in patients with heart failure and systolic dysfunction.

METHODS

The MOCHA trial was a six-month, double-blind, placebo-controlled, randomized, multicenter, dose-response evaluation of carvedilol in 345 patients with chronic stable symptomatic

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ASA = aspirin
EF = ejection fraction
HR = heart rate
LVEF = left ventricular ejection fraction
MCL = multicollinearity
MOCHA = Multicenter Oral Carvedilol Heart failure Assessment
PG = prostaglandins

heart failure (14). Patients were randomized uniformly into four groups: 1) placebo, 2) low-dose carvedilol (6.25 mg twice daily), 3) medium-dose carvedilol (12.5 mg twice daily) and 4) high-dose carvedilol (25 mg twice daily). The specific methods and results of this trial have been reported (14). Patients underwent a baseline radionuclide LVEF during a three-week screening phase when eligibility for the study was determined. Once eligibility was determined and informed consent given, patients underwent a two-week challenge phase consisting of an initial dose of 6.25 mg twice daily of carvedilol. This dose could be decreased to 3.125 mg twice daily as necessary for symptoms of hypotension or worsening heart failure; if the dose was initially decreased to 3.125 mg twice daily, it was increased to 6.2 mg twice daily in the second week of the challenge phase. Patients must have tolerated the 6.25-mg twice daily dose to be randomized. Up-titration of carvedilol was carried out on a weekly basis and most patients reached maximum dose in two weeks, although patients having difficulty could take four weeks to reach a maximum dose. Following the up-titration phase, there was a six-month maintenance phase. The radionuclide LVEF was repeated at the end of the maintenance phase.

According to study design, all patients were between 18 and 85 years of age and had an LVEF of ≤35% with symptomatic heart failure of either ischemic or nonischemic etiology. The patients had to have symptoms of heart failure for at least three months and a 6-min walk test of 150 m to 425 m (revised upward to 150 m to 450 m by protocol amendment six months into the study). A resting heart rate of ≥68 beats/min in the sitting position was required for study participation.

All randomized patients who had evaluable ejection fraction (EFs) at baseline and end of study (n = 293) were evaluated. Inter-LVEF intervals averaged 8 months, ranging from 4 to 12 months, with 280 of the 293 intervals (96%) from 7 to 9 months. Patients were compared according to dose of ASA taken at baseline. Determinations of all baseline medications were from the MOCHA file of current medications and identified by drug code.

All analyses were performed with SAS software (SAS Institute, Cary, North Carolina). Statistical significance was set at a two-sided alpha = 0.05. Unless otherwise specified, data are presented as mean ± SEM. Baseline comparisons of ASA nonusers and users was by chi-square test and unpaired *t* test. Bivariate comparisons of changes in LVEF, heart rate (HR) and systolic blood pressure, between ASA nonusers and users, broken down by carvedilol use and etiology (ischemic vs. nonischemic), were by unpaired *t* test or Wilcoxon Rank Sum test. The primary end point in analysis was the change in LVEF. The multivariate design, though balanced by etiology and carvedilol dose, was unbalanced by ASA use, as might be expected in a retrospective analysis. To analyze the effect of ASA dose, controlling the effects of etiology and carvedilol dose, multivariate analyses were performed, using the general linear model procedure of SAS. Adjusted means (as would be expected had the design been balanced) and their standard errors were calculated with the LSMEANS statement.

Table 1. Demographics

	ASA Nonusers	ASA Users	p Value
Descriptor			
n	178	115	
Age (yr)	58 ± 1	62 ± 1	0.002
Heart rate (beats/min)	84 ± 1	80 ± 1	0.02
Gender (% male)	72	83	0.046
NYHA II/III/IV (%)	48/49/3	47/52/1	0.50
Cause of CHF (% ischemic)	34	75	0.001
Race (% white)	74	83	0.07
Carvedilol dose (%) 0/6.25/12.5/25 mg twice daily	19/30/25/26	25/18/26/30	0.11
EF (EF units)	23 ± 1	24 ± 1	0.39
Current medications (%)			
ACE inhibitors	96	89	0.02
Digoxin	93	90	0.35
Loop diuretics	96	97	0.67
Thiazide diuretics	22	20	0.62
Vasodilators	46	65	0.001
Coumadin	75	23	0.001
Calcium channel blockers	1	2	0.33

ACE = angiotensin-converting enzyme; ASA = aspirin; CHF = congestive heart failure; EF = ejection fraction; NYHA = New York Heart Association.

The multiple linear regression initially considered 18 predictor variables having theoretical plausibility: duration of congestive heart failure, baseline systolic blood pressure and all variables listed in Table 1, as well as ASA usage in milligrams per day. Additional current medications were treated as binary variables. For the predictors of primary interest (ischemic etiology, carvedilol dose, ASA dose), the four interactions were also included. Predictor variables were removed from the model in stepwise backwards elimination fashion, using the least significant criterion with alpha = 0.05.

Expected positive correlation between ASA use and ischemic etiology and possible correlation between ASA use and carvedilol dose raised multicollinearity (MCL) (high linear dependence among one or more independent variables) concerns. Diagnostics used for MCL were the bivariate correlation coefficient, the variance inflation factor and the condition index (15,16). Values suggesting MCL are variance inflation factor ≥ 10 and condition index ≥ 30 (16).

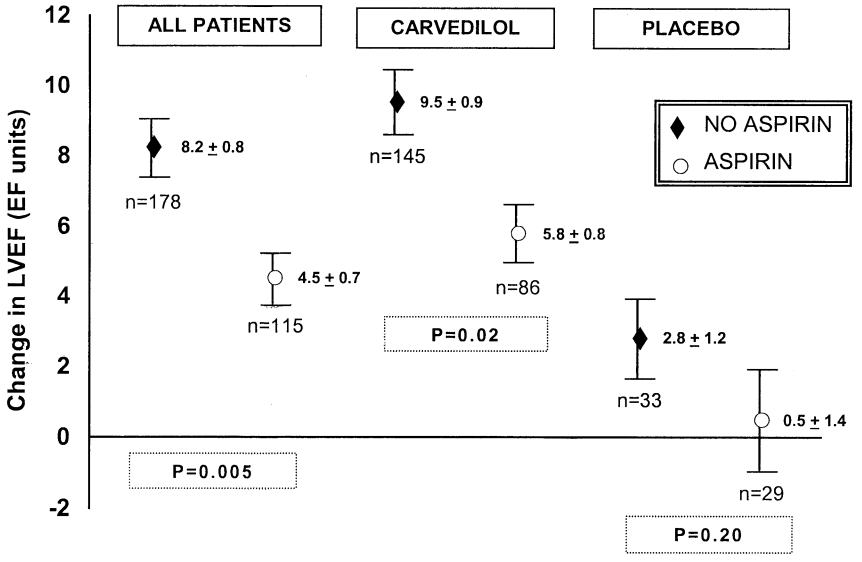

Figure 1. Changes in left ventricular ejection fraction (LVEF) in all patients, in carvedilol-treated patients and in placebo-treated patients.

RESULTS

Table 1 gives important baseline descriptors of the patients. There were 231 patients randomized to treatment with carvedilol and 62 patients randomized to treatment with placebo: 178 were ASA nonusers and 115 were ASA users. The ASA nonusers were younger than ASA users (58 ± 1 year vs. 62 ± 1 year, p = 0.002) and had a higher resting HR (84 ± 1 beats/min vs. 80 ± 1 beats/min, p = 0.02). Systolic blood pressure was not different, averaging 115 mm Hg. The LVEF was not different, averaging 23 EF units.

More of the ASA users were male (83% vs. 72%, p = 0.05) and had an ischemic etiology of HF (75% vs. 34%, p = 0.001). Percentages of patients in New York Heart Association classes II, III and IV did not differ. Background medical therapy is also shown in Table 1. Most patients were taking ACE inhibitors, loop diuretics and digoxin. The ACE inhibitors were used slightly less often in ASA users than in nonusers (89% vs. 96%, p = 0.02). More of the ASA users were taking vasodilators, including nitrates (65% vs. 46%, p = 0.001). Twenty-three percent of the ASA users were taking coumadin compared to 75% of the non-ASA users (p = 0.001).

Change in LVEF in ASA nonusers and users is shown in Figure 1. The LVEF improved by 8.2 EF units in the ASA nonusers and by 4.5 EF units in the ASA users (p = 0.005). In the carvedilol group, ASA nonusers had a 9.5-EF unit increase compared to a 5.8-EF unit increase in the ASA users (p = 0.02). In the placebo group, LVEF improved by 2.8 EF units in the ASA nonusers compared to a 0.5-EF unit increase in the ASA users (p = 0.20)

Change in HR is shown in Figure 2. Overall patients' HRs decreased 11 beats/min with no differences according to ASA use. The HR decreased 14 beats/min in the carvedilol-treated patients and 2 beats/min in the placebo-treated patients; there were no differences in the ASA users versus nonusers. Systolic blood pressure showed no significant differences according to ASA use (Fig. 3). In Figure 3, the interaction of carvedilol use (placebo, carvedilol) and ASA use (no ASA, ASA) was not significant.

Mean values of the change in LVEF were further broken down by etiology (ischemic vs. nonischemic) and treatment group (carvedilol vs. placebo) and are shown in Table 2. Although no significant differences by aspirin use resulted, ASA users had a consistently lower improvement in LVEF compared to nonusers, by 1.6 to 2.5 EF units.

Results of multiple linear regression are shown in Table 3. In this Table, "b value" gives the change in LVEF for each unit change in the associated predictor, while controlling the effect of all other predictor variables. Thus, ASA dose is significant at p = 0.0005, with an expected decrease of 0.5 EF units in LVEF for each increase of aspirin dose of 81 mg/d. Ischemic etiology is significantly associated with a decrease of 3.4 EF units, relative to nonischemic etiology. Effects shown in Table 3 are additive. For example, an ischemic subject taking 325 mg/d of ASA is expected to have a change in LVEF that is 5.4 ($3.4 + 4 \times 0.5$) EF units lower than a nonischemic subject not taking ASA. In Table 3, only three variables have significance stronger than marginal: ischemic etiology, carvedilol dose and ASA dose. None of the four interactions of these variables was significant, the strongest being the interaction of ischemic etiology and carvedilol dose (p = 0.07). These results are consistent with the results of the analysis of LVEF in the MOCHA trial, which showed a dose-response relationship of carvedilol dose and LVEF (p = 0.001) and showed that the response was stronger for nonischemic etiology than for ischemic etiology (p = 0.068) (14). In Table 3, b for baseline LVEF is negative and b for baseline HR is positive, consistent with a theorized normalizing action of carvedilol:

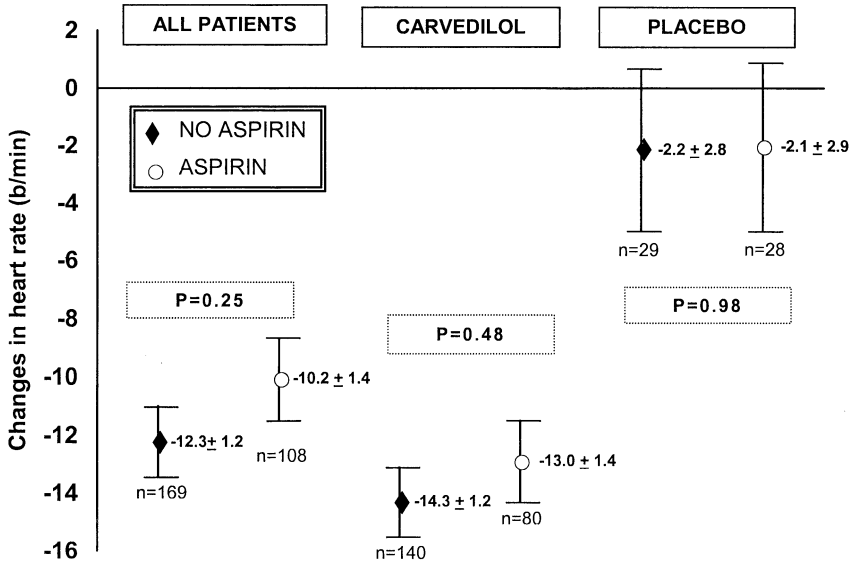

Figure 2. Changes in heart rate. Groups as in Figure 1.

a lower baseline LVEF or a higher baseline HR results in greater benefit of carvedilol. Out of concern for MCL, regression diagnostics (maximum absolute value bivariate correlation coefficient, maximum variance inflation factor, maximum condition index) were used. For the model with six independent variables (Table 3), the values were 0.31, 1.17 and 1.61, respectively. For the model with three independent variables (ischemic etiology, carvedilol dose, ASA dose), the values were 0.13, 1.03 and 1.20, respectively. None of these diagnostic values indicates the presence of MCL. Figure 4 shows graphically the results of multiple regression analyses of change in LVEF on carvedilol dose and ASA use, separately by ischemic etiology. The slopes are nearly equal, with change in LVEF being about 3 EF units less for ischemic etiology than for nonischemic etiology, consistent with the MOCHA findings (14).

DISCUSSION

This study shows that in heart failure patients taking carvedilol, LVEF improves less in patients taking ASA than in patients not taking ASA. This result is not simply due to the greater use of ASA in patients with an ischemic etiology as multivariate analyses show that the negative effect of ASA is independent of the negative effect of ischemic etiology, with this independent effect validated by the

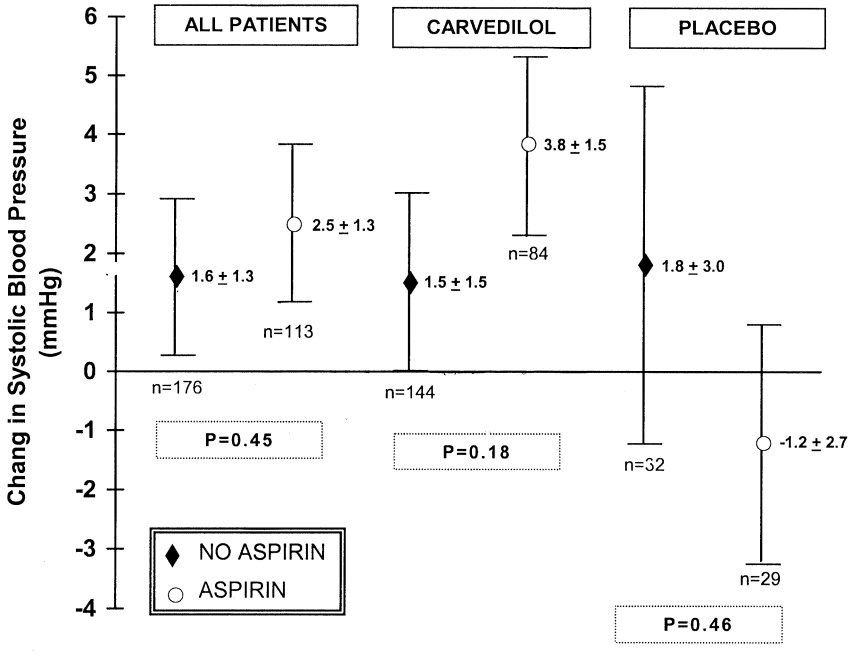

Figure 3. Changes in systolic blood pressure. Groups as in Figure 1.

Table 2. Changes in Left Ventricular Ejection Fraction by Etiology, Carvedilol Use and ASA Use

	n	Changes in EF Units	p Value	Difference in ASA Users vs. Nonusers
Ischemia				
Placebo				
ASA Nonusers	15	0.9 ± 2.0	0.45	−2.0
ASA Users	17	−1.1 ± 1.6		
Carvedilol				
ASA Nonusers	45	7.6 ± 1.3	0.09	−2.5
ASA Users	69	5.2 ± 0.8		
Nonischemia				
Placebo				
ASA Nonusers	18	4.4 ± 1.2	0.49	−1.6
ASA Users	12	2.7 ± 2.3		
Carvedilol				
ASA Nonusers	100	10.3 ± 1.1	0.57	−1.6
ASA Users	17	8.6 ± 2.3		

ASA = aspirin; EF = ejection fraction.

absence of MCL in the model. Further, the effect of ASA was dose-related.

From Table 3, the effect of ischemic etiology on the change in LVEF is −3.4 EF units and the effect of ASA at 325 mg/d on the change in LVEF is calculated to be −2.0 EF units, about half the effect of ischemic etiology and biologically important. Expressed as ratios, the effects of ASA correspond to 20% to 30% reductions in the beneficial effect of carvedilol. Etiology of heart failure, ASA dose and carvedilol dose were all strong predictors of the change in LVEF and test results for interaction among these variables were nonsignificant. It is important to note that the combination of carvedilol and ASA appears to limit but not prevent an improvement in LVEF.

The apparent effect of ASA on change in LVEF in patients taking placebo was unanticipated. Although this effect was not significant, it was similar to the change seen in carvedilol-treated patients. For placebo-treated patients as a separate group, the smaller change in LVEF and the smaller n reduced the statistical significance of the effect of ASA, making it equivocal. Further studies evaluating changes in LVEF and ASA in the absence of beta-blockers are warranted.

Potential mechanisms. There are two explanations for the finding the LVEF improved less with carvedilol in patients taking ASA. Aspirin may interfere with a mechanism of benefit of carvedilol on LVEF. Conversely, ASA and carvedilol might share a mechanism for some of the beneficial effect in LVEF, so that some improvement in EF would have already occurred in the patients taking ASA, leaving less potential for improvement in LVEF with carvedilol. Data in hypertensive patients suggest that ASA blunts the hypotensive but not the negative inotropic and chronotropic effects of beta-blockers (13). Indeed in the present study, ASA use had no effect on the substantial negative chronotropic effect of carvedilol. While there was a trend for ASA use to have a positive effect on change in systolic blood pressure in carvedilol-treated patients and a negative effect in placebo-treated patients (Fig. 3), this interaction was not significant. Data on systemic vascular resistance were not available.

Table 3. Multivariate Analysis of Factors Influencing the Change in LVEF

Predictor	Unit	b Value	p Value
Ischemic etiology	—	−3.38	0.0002
Carvedilol dose	+6.25 mg twice daily	+1.91	0.0001
Aspirin dose	+81 mg every day	−0.51	0.0005
Baseline LVEF	+10 EF U	−1.45	0.03
Baseline HR	+10 beats/min	+0.70	0.04
Use of coumadin	—	−2.34	0.03

EF = ejection fraction; HR = heart rate; LVEF = left ventricular ejection fraction.

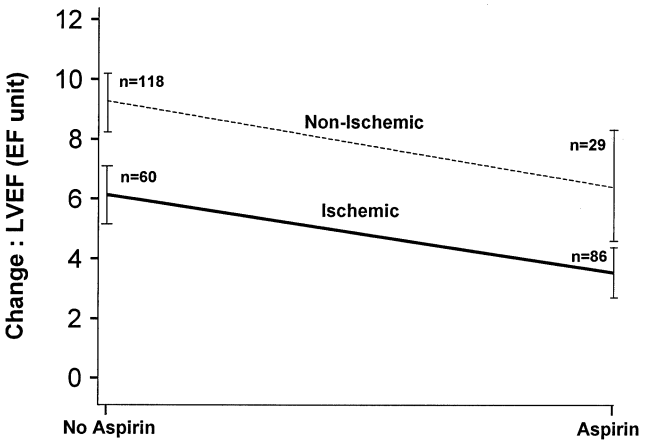

Figure 4. Change with left ventricular ejection fraction (LVEF) in aspirin users and nonusers.

There are at least three potential mechanisms of interaction between carvedilol and ASA in patients with heart failure. Recently it has been shown that treatment with beta-blockers in patients with hypertension and heart failure is associated with an elevation in natriuretic peptides which would be likely to have a beneficial effect promoting reverse myocardial remodeling (17–19). This effect is not simply a result of myocardial stretching and has been postulated to be a mechanism by which beta-adrenergic blockers may result in improvements in myocardial function (19,20). Natriuretic peptides are released by prostaglandin $F_{2\alpha}$ in isolated cardiac myocytes (21,22). Aspirin, by preventing the synthesis of prostaglandin $F_{2\alpha}$, could diminish the release of natriuretic peptides caused by beta-blockers limiting one potential beneficial effect of carvedilol on LVEF. If this interaction is operative, ASA might block some of the potential benefit of carvedilol on LVEF.

A second possible site of interaction is at the sympathetic nerve terminal. It is known that the bradykinin-stimulated release of norepinephrine from cardiac sympathetic nerves is inhibited by cyclo-oxygenase inhibition (23–25). Bradykinin levels are increased in heart failure patients taking ACE inhibitors (26,27). Aspirin, through cyclo-oxygenase inhibition, might diminish bradykinin-mediated cardiac sympathetic activity limiting another potential benefit of beta-

blockers. Indeed Wang (28) has shown an enhanced renal sympathetic nerve activity in response to epicardial bradykinin administration in a dog model of heart failure. The bradykinin-enhanced renal sympathetic nerve activity was decreased by cyclo-oxygenase inhibition. In this situation, ASA might cause an improvement in LVEF in patients with heart failure by decreasing cardiac sympathetic nerve activity, leaving less room for a benefit of carvedilol in blocking cardiac beta-adrenergic receptors.

A third potential site of interaction occurs because ASA and beta-blockers inhibit renin release, especially in clinical situations such as heart failure in which renin is activated (18,29,30). It is possible that ASA lowers renin levels, thus reducing the magnitude of the beneficial effect of beta-blockers on renin. In this case, as in the previous situation, ASA would have already provided some the benefit of carvedilol on LVEF.

The present study cannot determine the mechanism for the interaction of ASA and beta-blockers on LVEF. We also cannot determine if ASA and carvedilol share a common beneficial effect on LVEF or if ASA blocks a beneficial effect of carvedilol. However, one previous study as well as our own study suggest that ASA and carvedilol may share a common mechanism of benefit. In a retrospective analysis of the Captopril And Thrombolysis Study (CATS), Oosterga et al. (12) found that ASA alone reduced left ventricular dilation independently of ACE inhibitors. This finding suggests that ASA alone may result in beneficial effects on LVEF. Although not statistically significant, in this study there was a trend for less improvement in LVEF in the placebo group in the ASA users than in the non-ASA group. This might also suggest these patients had already had a beneficial effect of ASA on LVEF. To our knowledge, this the first study to describe an interaction between ASA and beta-blockers in ventricular remodeling. This interaction was strong and was enhanced in a multivariate analysis. The mechanism by which beta-blockers improve myocardial function in patients with heart failure is unknown. Further investigation of the interaction between beta-blockers and ASA may shed light on the mechanism(s) of myocardial remodeling (31).

Impact on mortality. This study was too small to assess the effect that ASA might have on the improved mortality seen with carvedilol. It is not clear if an improvement in LVEF with beta-blockers could be used as a surrogate for the mortality benefit, although data from Cardiac Insufficiency Bisoprolol Study suggests that this may be the case (32). Our study suggests that a dose of 325 mg/d of ASA might result in 2 EF units less in improvement with carvedilol. This small difference in EF has been associated with a difference in mortality (14,33). However, even if the improvement in LVEF is etiologic in the benefits of beta-blockers on mortality, other beneficial effects of ASA may have a balancing effect on mortality. Thus, it is not possible to conclude that aspirin might limit the beneficial mortality effect of beta-blockers in patients with heart failure.

Aspirin dose. In this study most of the patients taking ASA (71%) were taking a dose of 325 mg/d. However, we have shown a dose-related effect of ASA on the improvement in LVEF seen with beta-blockers. Although low doses of ASA are believed to have a short-lived effect on endothelial prostacyclin production, ASA in doses of 40 to 80 mg given to patients 12 to 16 h prior to coronary bypass surgery suppresses aortic prostacyclin production by 35% to 38% (34). In addition, the effect of low doses of ASA on prostacyclin production and the duration of that effect may be different in nonvascular endothelial tissues (35). Myocardial cells and endocardial endothelial cells are known to synthesize PGs PGI_2, PGE_2 and $PGF_{2\alpha}$, but the duration of effect of ASA on cyclo-oxygenase and the dose of ASA required for this effect in these tissues are unknown (36,37). A recent study in human subjects with heart failure demonstrated that even 75 mg of ASA blocked arachidonic acid–induced vasodilation (38). Thus, substantial data indicate that even low-dose ASA could influence some of the potential mechanisms of myocardial remodeling.

Consistency of the findings. The findings of this article are strengthened by their consistency. The clinical effect of a loss of 2 EF units of change in LVEF, for a dose of 325 mg/day of ASA, was seen repeatedly: across etiology (ischemic, nonischemic), across beta-blocker treatment (placebo, low-dose, mid-dose, high-dose) and across type of analysis (bivariate, multivariate). The strongest predictors influencing the change in LVEF with carvedilol were carvedilol dose, ASA dose and etiology of heart failure. Carvedilol dose and ischemic etiology have both been shown to be important predictors of the improvement in LVEF with beta-blockers (14,39). Baseline LVEF, baseline HR and coumadin were weaker predictors. Baseline LVEF and HR were shown to be similar predictors in a previous analysis (30). Coumadin has not been reported to be a predictor of change in LVEF. However, the statistical strength of this association was relatively weak. The association cannot be explained by the greater coumadin use in nonischemic patients, as coumadin in multivariate analysis was found to be associated with less improvement in LVEF with carvedilol, not more as would be expected if coumadin identified nonischemic patients. Further study of the effects of coumadin is clearly necessary.

Study limitations. This study is limited by its retrospective nature. It is further limited by baseline differences between ASA users and nonusers, particularly in age and etiology, resulting in correlations among predictor variables. While there was no MCL, multivariate analysis may not have completely controlled these differences. Despite the small number of subjects, highly significant results were found.

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